5. (Amended) A composition according to claim 1, wherein said end parts further comprise a [comprising] mutually chemically reactive compound [compounds at said end parts].

6. (Amended) A composition [according to any] as in one of claims 1-5, wherein said padlock probe comprises a non-natural nucleic [acids or polymers] acid or polymer.

7. (Amended) A composition for targeting a double stranded nucleic [acids, comprising] acid, wherein said composition comprises an effective amount of a padlock probe oligonucleotide having two free nucleic acid end parts which [are at least partially complementary] anneal to [and capable of hybridizing with] two [at least substantially neighboring respective regions of a target] closely adjacent sequences within said double stranded nucleic acid [sequence] so that [it can be circularized] the padlock probe is capable of circularization by joining said free end parts and [catenate] catenating with a [the] target sequence within said double stranded nucleic acid, for [use as a medicament] inhibition of replication.

REMARKS

Claims 1-7 are currently pending. Pending claims 1-7, as amended herein, are enclosed as an attachment.

Amendments to Claims 1-7 are made for clarity and/or as further detailed below.

Support for the amendment of Claim 1, reciting the term "transcription" is found in the specification, e.g., on page 4, line26, and on page 8, Example 2.

Support for the amendment of Claim 7, reciting the term "replication" is found in the specification, e.g., on page 4, line 26.

No new matter was introduced as of these amendments.

The objection of Claims 6 under 37 CFR 1.75

The Examiner objects to Claim 6 as being in improper multiple dependent form. Applicant herewith has amended Claim 6 and submits that it is now conforming with proper claim dependency.

The rejection of Claims 1-5 under 35 U.S.C. §112, first paragraph:

The Examiner rejects Claims 1-5 under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to make and/or use the invention. Specifically, the Examiner notes that Applicant recites "a pharmaceutical composition" in the rejected claims and asserts that the issue is that the claims are "directed towards the use of oligonucleotides as a pharmaceutical agent". Accordingly, the Examiner contends that the issue then becomes "irreproducibility of results, when using oligonucleotides, for example, in cellular uptake or in unanticipated nonspecific effects and in attempts to translate results obtained by *in vitro* experimentation to *in vivo* models."

Applicant respectfully traverses this rejection. Applicant submits that the claims are drawn to "A pharmaceutical composition for targeting a double stranded nucleic acid wherein said composition comprises an effective amount of a padlock probe oligonucleotide having two free nucleic acid end parts which anneal to two closely adjacent sequences within said double stranded nucleic acid so that the padlock probe is capable of circularization by joining said free end parts and catenating with a target sequence within said double stranded nucleic acid for direct inhibition of transcription." (Emphasis added).

Applicant submits that the articles cited by the Examiner are not substantive references addressing the subject matter of the present invention and as such can not be used in rejecting the above claims. Generally the cited references are concerned with the use of oligonucleotides targeting RNA and not DNA, as recited in the present claims. The articles further do not address

oligonucleotides that (i) hybridize with two closely apposed sequences within a double stranded nucleic acid, (ii) which are capable of circularization by joining said free end parts and (iii) catenate with a target sequence within a double stranded nucleic acid.

For example, the first reference (Nature Biotechnology 15, 519-528, 1997), which is excerpted from "the transcript of a one-hour roundtable discussion", addresses the major themes emerging from that discussion. As pointed out above, it seems, that during this round table discussion, primarily the effect of oligonucleotides on antisense inhibition of RNA was addressed (see page 520, 3rd column, last paragraph):

> "The concern is with how one selects the site on the RNA that is really the best for the binding of the antisense, or a ribozyme, for that matter." (Emphasis added).

Thus, the subject matter of this discussion seems to be unrelated to the present invention. However, in as far as the subject matter of this discussion can be applied to the present invention, in particular with respect to (i) delivery, (ii) specificity, (iii) effectiveness, and (iv) a good correlation between *in vitro* and *in vivo*, Applicant notes that the above cited reference contains multiple passages, wherein delivery, specificity, effectiveness, and a good correlation between *in vitro* and *in vivo* data is acknowledged:

e.g., page 519, column 1:

> "This meeting was remarkable for the number of examples of antisense specificity and effectiveness in whatever model system was explored.";

e.g., page 520, column 1:

> "The other thing is, as we have seen with all of these oligos, if you are able to alter gene expression within cells, particularly the genes related to malignant cells, I think you can show that there is a very good synergy with conventional therapy."

e.g., page 520, column 2:

> "In the areas of delivery, formulation, length of treatment, and long-term toxicity, the profile is being established."

e.g., page 521, column 1:

> "He actually showed some of the most brilliant data that we saw here. He actually showed the disruption of target-gene expression in lymphoma cells from patients treated with anti-BCL2 oligonucleotide. .... who has actually demonstrated some efficacy in vivo through inhibition of target-gene expression."

e.g., page 521, column 3:

> "There have been a number of studies in the central nervous system that show a great deal of specificity for the antisense oligonucleotides. There are studies, particularly in the dopamine system, in which an antisense directed to the D1 dopamine receptor message only inhibits D1 response and not D2 responses. There are D2 antisenses that only block D2 responses and not D1 responses. So I think that a great deal of selectivity has been demonstrated in some in vivo studies using antisense oligonucleotides."

e.g., page 522, columns 1 and 2:

> "A long time ago he showed that with a ras oligo against the mutant, you could discriminate between wild type and mutant. It was a beautiful paper. I mean, hundreds of data points, error bars, it was irrefutable. And I personally have repeated that data. I have used it many many times. It works every time I do it."

page 522, column 3:

> "... is that inhibition of gene expression, .. can be highly reproducible in vivo..."

page 523, column 1:

> "I was gratified to see in this meeting that there is a lot of good correlation between in vitro behavior and in vivo pharmacokinetics and activity."

The second reference (Antisense Research and Development 4:67-69, 1994) is an editorial, providing the policy of the respective journal with respect to the interpretation of data obtained in antisense experiments. This reference further describes some characteristics of phosphorothioate (PS) oligonucleotides, which appear to block the binding of bFGF and PDGF to their cognate receptors and which appear to interact with some cellular proteins. It is

acknowledged that the above effects described for PS oligos are not observed with phosphodiester oligos. As such, Applicant submits that any attempts to apply the effects mediated by PS oligos to the oligonucleotides of the present invention, are equally not warranted.

The third reference (Science 170:575-577, 1995), and as it seems references 1, 2, and 4 as well, consider oligonucleotides of about 20 DNA bases as the composition to be employed in antisense applications. However, according to the specification, the oligonucleotides of the present invention are (a) much longer (generally approximately 90 nucleotides) than standard oligonucleotide currently used for antisense applications, (b) target double stranded DNA, instead of RNA, and (c) interact with the target DNA in a way no other oligonucleotide has been shown to interact; they can be circularized and catenate with the targeted DNA region. The unique design and its interaction with the target DNA, also sets the claimed subject matter apart from oligonucleotides employed in so-called "triplex" technologies. Thus, Applicant submits that the subject matter discussed in the above-cited references does not warrant a valid analogy to the composition claimed in the instant application.

The fourth reference (TIBS 23:45-50, !998) considers only antisense molecules and ribozymes designed to inhibit RNA targets. As pointed out above, the present invention provides for oligonucleotides targeting double stranded DNA. (Emphasis added).

In addition, Applicant submits that it is well documented in the art to successfully apply antisense technology *in vivo*, e.g.,

1). Kasuya et al., Endocrinology 140:705-12, (1999);

2). Ohmichi et al., Development 125:1315-24, (1998);

3). Rubenstein et al., Methods Find exp. Clin. Pharmacol. 20:825-31 (1998);

4). Bilsky et al., Neurosci Lett. 220:155-8 (1996);

5). Lai et al., Neurosci. Lett. 213:205-8 (1996)

6). Bilsky et al., J. Pharmacol. Exp. Ther. 277:491-501 (1996);

7). McCarthy et al., Regul. Pept. 59:163-70, (1995);

8). Bilsky et al., J. Pharmacol. Exp. Ther. 273:359-66 (1995);

9). Tseng et al., Eur. J. Pharmacol. 258:R1-3, (1994);

10). McCarthy et al., Brain Res. 636:209-20 (1994);

11). Bilsky et al., Life Sci. 55:PL37-42 (1994);

12). Lai et al., Neuroreport 5:1049-52 (1994);and

13). Heilig et al., Eur. J. Pharmacol. 236:339-40 (1993).

Abstracts of the above-cited references accompany this amendment. Thus, as far as it concerns (i) delivery of oligonucleotides *in vivo*, (ii) effective amounts of oligonucleotides, and (iii) effect of said oligonucleotides on gene expression *in vivo*, the skilled artisan is provided with sufficient guidance.

In summary, Applicant submits that the references cited by the Examiner either do not apply to the claimed subject matter or, in fact, as outlined above, support Applicant's invention. Further Applicant submits, that given the guidance provided by the references cited by the Applicant and the instant application, a skilled artisan would not have to practice undue and excessive experimentation and as such would be enabled to make and/or use the invention. Accordingly, the Applicant respectfully request reconsideration and withdrawal of the rejection of record.

The rejections of Claim 7 under 35 U.S.C. §102(b):

The Examiner rejects Claim 7 under 35 U.S.C. §102(b) as being anticipated by Nilsson et al. (Science 265:2085-2088, 1994). The Examiner contends that the composition of Claim 7 is disclosed in Nilsson et al. and that the instant claim recites an "intended use" which can not be accorded any weight in determining patentability.

Nilsson et al. describe several complexes between an oligonucleotide and certain nucleic acid molecules: e.g., (i) an oligonucleotide complexed with single-stranded DNA (page 2085, column 3 and Figures 1and 2; (ii) an oligonucleotide binding to single-stranded DNA immobilized on nylon membranes (page 2086, column 3 to page 2087, column 1 and Figure 3; an oligonucleotide binding under *in situ* hybridization condition to denatured DNA (page 2087, column 1 and Figure 4); (Emphasis added). For an invention to be anticipated under 35 U.S.C. §102(b), the cited reference must teach every element of the claim (MPEP §2131). In accordance with the specification, Applicant has amended Claim 7 to recite "...catenating with a target sequence within said double stranded nucleic acid,...inhibits replication." There is nothing in Nilsson et al. that would anticipate or suggest that the padlock probe oligonucleotide of the present invention (i) targets double-stranded nucleic acid, (ii) catenates with a target sequence within said double stranded nucleic acid and (iii) inhibits replication. Accordingly, Applicant respectfully request withdrawal of the rejection of record.

The rejections of Claims 1, 3, 5, and 7 under 35 U.S.C. §112:

The Examiner rejects claims 1, 3, 5, and 7 under 35 U.S.C. §112 as being indefinite for failing to point out and distinctly claim the subject matter which applicant regards as the invention.

Specifically, the Examiner considers Claim 1 vague in the recitation of the phrase "characterized in that." Following the Examiner's suggestion, Applicant has replaced the term "characterized in that" with the term "wherein said composition." Applicant thanks the Examiner for his helpful suggestion.

The Examiner considers Claims 1 and 7 vague with respect to the recitation of the phrase "an effective amount", which he notes is not further defined by the claim. Applicant has amended Claims 1 and 7 to recite "...for direct inhibition of transcription" and "... for inhibition of replication." and thus provides a definition of "an effective amount."

The Examiner contends that the recitation of the phrases "are at least partially complementary to and capable of hybridizing with" and "with two at least substantially neighboring respective regions" renders Claims 1 and 7 indefinite. The Examiner suggests to replace the above phrases with "hybridize" and "with two closely apposed sequences." Applicant has amended Claims 1 and 7 similarly, by reciting the phrase "anneal to two closely adjacent sequences."

The Examiner considers Claim 7 vague for reciting an intended use for a claimed composition. In response thereto, and, in addition to the amendments detailed herein, Applicant has amended Claim 7 accordingly. The phrase "for use as a medicament" is deleted.

The Examiner considers Claim 3 vague for reciting "linking agent" and not pointing out what will be linked by the linking agent. As disclosed in the specification, e.g., on page 4, lines 14-22, the probe ends are circularized by ligase. The specification provides further on page 5, lines 11-15:

> "c) circularization of said padlock probe by joining said free end parts.
> The joining in step c) is performed with a linking agent such as a ligase enzyme or mutually chemically reactive compounds at the free end parts."

In accordance with the specification, Applicant has amended Claim 3 for clarity.

The Examiner objects to claim 4 reciting the phrase "wherein linking agent". Following the Examiner's suggestion, Applicant has amended Claim 4 to recite "wherein said linking agent."

In conclusion, Applicant has amended the rejected claims in accordance with the specification and following the Examiner's suggestions. Accordingly the rejections of record should be withdrawn.

The Applicant submits that the claims are now in condition for allowance and an early notification of such is respectfully solicited.

If after review of this amendment, the Examiner has further unresolved issues, the Examiner is respectfully requested to phone the undersigned, Richard Trecartin, at (415) 781-1989.

Respectfully submitted,

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Claims as of Response to Office Action (dated August 5, 1999)

1. (Amended) A pharmaceutical composition for targeting a double stranded nucleic acid wherein said composition comprises an effective amount of a padlock probe oligonucleotide having two free nucleic acid end parts which anneal to two closely adjacent sequences within said double stranded nucleic acid so that the padlock probe is capable of circularization by joining said free end parts and catenating with a target sequence within said double stranded nucleic acid for direct inhibition of transcription.

2. (Amended) A composition according to claim 1, further comprising a suitable carrier.

3. (Amended) A composition according to claim 1, further comprising a linking agent, wherein said linking agent is capable of joining said two free nucleic acid end parts.

4. (Amended) A composition according to claim 3, wherein said linking agent is a ligase enzyme.

5. (Amended) A composition according to claim 1, wherein said end parts further comprise a mutually chemically reactive compound.

6. (Amended) A composition as in one of claims 1-5, wherein said padlock probe comprises a non-natural nucleic acid or polymer.

7. (Amended) A composition for targeting a double stranded nucleic acid, wherein said composition comprises an effective amount of a padlock probe oligonucleotide having two free nucleic acid end parts which anneal to two closely adjacent sequences within said double stranded nucleic acid so that the padlock probe is capable of circularization by joining said free end parts and catenating with a target sequence within said double stranded nucleic acid, for inhibition of replication.